IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and ASTEX THERAPEUTICS LTD. Plaintiffs, v. MSN PHARMACEUTICALS INC. and MSN LABORATORIES PVT. LTD., Defendants.	C.A. No. 21-870-GBW (CONSOLIDATED)

MSN'S POST-TRIAL FINDINGS OF FACT

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March 1, 2024

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I. BACKGROUND

A. State of the Art

1. Cyclin-dependent kinases ("CDKs") control transitions from one phase of the cell cycle to another, the cycles are critical for cell division. JTX0096-0001-0002 and 0002-0003; Tr. 48:8-17 (Micalizio), 358:6–359:13 (Toogood).

2. CDK4 was identified as a potential drug target, and by 2004, it was known that compounds specifically inhibiting CDK4 exhibited efficacy in *in vivo* tumor models. JTX0093-0001 (r. col., ¶2); Tr. 48:18-50:11 (Micalizio), 492:2-20 (Toogood).

3. Pfizer's compound PD 0332991, now called palbociclib, was identified in 2004 as one of the potent inhibitors of CDK4/6 that exhibited antitumor activity. Tr. 48:18–50:11 (Micalizio), 492:2-9 (Toogood); JTX0093-0009 (r. col., ¶2).

4. Before 2006, a POSA understood the active regions of CDK4, how to design ligands to target them, and specifically, that to inhibit CDK4, a POSA would target the ATP binding site. Tr. 52:11-17 (Micalizio), 360:1-15 (Toogood) ("They all bind to ATP.").

5. Before 2006, there was substantial structural information regarding CDK2, from which a POSA would know how to design CDK4 ligands. Tr. 53:3-9 (Micalizio); *see also* JTX0099-0002 (l. col., ¶3).

6. Before 2006, a POSA knew that the CDK4 ATP binding site could be divided into four subregions: (1) the hinge region, (2) the specificity surface, (3) the ribose/phosphate site, and (4) the Phe80 pocket. Tr. 53:10–55:1 (Micalizio); JTX0156-0002-0006.

7. A POSA would have known that an aminopyrimidine group was critical to form hydrogen bonds with the hinge region of the ATP binding site. Tr. 62:9–64:4, 64:24–65:23, 68:10–69:21 (Micalizio); JTX0021-0003 (l. col., ¶4-r. col., ¶1); JTX0096-0006 (¶2, FIG. 7).

8. A POSA would have understood that an aromatic group with a *para*-substituted basic heterocycle (i.e., piperazine) placed off the aminopyrimidine amine to interact with the specificity surface increases CDK4 potency. Tr. 66:6–17, 76:25–78:3 (Micalizio); JTX0021-0004 (l. col., ¶2); JTX0099-0003 (r. col., ¶3)-0004 (l. col., ¶1 and Table 3). A POSA would have also known that substituting a 2-pyridyl group for a phenyl group off the aminopyrimidine amine improves selectivity for CDK4. Tr. 80:2–82:7 (Micalizio); JTX0094-0002 (l. col., ¶2).

9. A POSA would have known that the ribose-phosphate site could accommodate a variety of large, cyclic, hydrophobic moieties, but that placing a cyclopentyl group at that site would reasonably provide superior balance of potency and selectivity for CDK4. Tr. 66:18–67:8, 82:8–23 (Micalizio); JTX0021-0004 (l. col., ¶ 3- r. col., ¶1; Tables 3 and 4); JTX0094-0003 (l. col., ¶4; Table 1).

10. A POSA would have known that small electron-withdrawing groups that interact with the Phe-80 pocket improves potency, and that an out-of-plane carbonyl-containing group at the Phe-80 pocket forms a favorable interaction with CDK4. Tr. 74:22–76:10, 83:2–84:9 (Micalizio); JTX0094-0003 (l. col., ¶5-r. col., ¶1; Table 2), -0005 (1. col., ¶1); JTX0099-0004 (l. col., ¶2), -0005 (Table 4).

11. A POSA would have understood that palbociclib is a potent and selective CDK4 inhibitor because of its optimal interactions with the four ATP binding site sub-regions. Tr. 80:4-15, 89:11-90:9 (Micalizio), 343:11-25 ("[Palbociclib] is a selective CDK4 inhibitor…"), 368:4-14, 371:14-372:9 (Toogood); JTX0094-0005 (1. col., ¶2).

B. <u>Novartis Created a "me too" Compound, Ribociclib</u>

12. In July 2005, Novartis began its CDK4 inhibitor project led by Dr. Christopher Brain and started its development reviewing the Pfizer SAR Papers. Tr. 226:22–227:6, 228:23–230:13, 243:17–244:1, 258:8–259:5 (Brain); JTX0020-0007-0015; JTX0024-00001. Dr. Brain's

team selected pyrrolopyrimidine compounds from Novartis's JAK3 program to modify into CDK4 inhibitors with the Pfizer SAR Papers as a guide. Tr. 236:11-13, 247:18–248:8, 253:7–255:7 (Brain); JTX0020-0031; JTX0022-0001-0002; JTX0095-0001-0002.

13. Novartis sought to use its less rigorous development approach to develop a "me too" compound to compete with Pfizer, resulting in filing of a provisional patent application on May 26, 2006, which matured into the '225 patent and was published as the Brain PCT. JTX0018-0003-0004; JTX0038-0004; JTX0039-0002; Tr. 237:12-15, 288:20–289:11, 290:16-25 (Brain); JTX0001-0002; JTX0042-00001.

14. The '225 patent and Brain PCT do not specifically disclose ribociclib, because it was indisputably not invented yet. Tr. 324:5-8 (Proffer); *see generally*, JTX-0001; JTX0042.

15. Novartis continued using the Pfizer SAR Papers to modify its pyrrolopyrimidine compounds to increase CDK4 selectivity. Tr. 262:24–265:9 (Brain); JTX0025-0001; JTX0026-0021-0024, -0046.

16. A POSA would have understood that a nitrogen-containing pyridyl group on the C2 side chain of palbociclib, rather than a carbon-containing phenyl group, affected CDK4 selectivity. Tr. 269:10-20, 271:19-22, 272:11-13, 283:17–284:5 (Brain); 499:24–500:4, 500:18-501:23 (Toogood); JTX0028-0001; JTX0029-0002; JTX0030-0001; JTX0031-0002, -0009; JTX0037-0009. Indeed, Novartis referred to this particular nitrogen as the "magic N." *Id.*

17. Due to the similarity of the compounds in the Pfizer SAR Papers, a POSA would have expected that insertion of a pyridyl group on pyrrolopyrimidine compounds with similar features would produce the same favorable selectivity. JTX0018-0004; Tr. 275:10–276:21, 284:8-15 (Brain); JTX0034-0001; JTX0037-0013.

18. The pyrrolopyrimidine called Compound 338 was conceived by Bharat Lagu, either alone or in combination with Yaping Wang, on January 16, 2007, and reduced to practice by Dr. Wang on January 25, 2007. JTX0040-0006; JTX0041-0069; Tr. 291:23–294:23, 296:20–297:8 (Brain).

19. On April 3, 2007, Dr. Brain conceived of ribociclib by replacing the phenyl group at the C2 position of Compound 338 with the "magic N" containing pyridyl group "[t]o improve the selectivity of [Compound 338]," and was reduced to practice on the same day. JTX0044-0029; JTX0045-0083; Tr. 294:10-23, 296:20-297:8, 304:24-305:19, 307:3-12, 309:10-310:7 (Brain); 323:15-324:8 (Proffer).

20. Expectedly, the replacement of the phenyl at C2 with the pyridyl would somewhat reduce potency for CDK4, but improve selectivity, so as to result in improved overall profile. JTX0026-0022; Tr. 263:24-264:5 (Brain); JTX0046-0001; Tr. 311:3-25 (Brain); *see* JTX0002-0011 (Table 4).

21. On August 22, 2008, Novartis filed a new provisional patent application that matured into the '630 and '355 patents. JTX0002-0002; JTX0004-0002.

22. The '630 and '355 patents' shared specification identifies three compounds from Brain PCT that "represent[s] the closest prior art to the chemotype of the presently claimed invention." JTX0002-0011; JTX-0004-0011. Compound 338 (listed as compound 200) is one of the three prior art compounds listed in the specification, as well as a table with the "inhibition against relevant targets of compounds of the prior art . . ." and "the results of cell cycle analysis performed with the presently claimed [ribociclib] and [C]ompound [338] of the prior art." *Id* at 0011-0012; Tr. 91:4-92:5 (Micalizio).

II. CLAIM 1 OF THE '355 PATENT AND CLAIM 6 OF THE '630 PATENT ARE OBVIOUS OVER COMPOUND 338 IN VIEW OF THE PFIZER SAR PAPERS

23. Asserted claim 1 of the '355 patent and claim 6 of the '630 patent are directed to the compound ribociclib and its use to treat carcinoma of the breast. JTX0002-0072 (claim 1); JTX0004-0073 (claim 6).

A. Compound 338 and Associated Statements are Admitted Prior Art to the '355 and '630 Patents

24. One of the three (and one of the two after concluding prosecution) of the prior art compounds repeatedly disclosed in the shared specification of the '355 and '630 patents is Compound 338. JTX0002-0011-0012; JTX-0004-0011-0012; JTX0007-4315; Tr. 90:19-92:16 (Micalizio); *see also* JTX0007-4315 (disclaiming one of the three compounds as prior art, but not Compound 338).

1. Compound 338 is the work of another

25. Dr. Brain alone conceived of ribociclib. *Supra.* ¶ 19. Dr. Lagu alone, or in collaboration with Dr. Wang, conceived of Compound 338. *Supra.* ¶ 18.

2. The scope of admitted prior art Compound 338

26. The '355 and '630 patents' joint specification not only identifies Compound 338 (among others) as prior art, but also identifies Compound 338 as "from" Brain PCT, identified by its application number, which "generically discloses compounds of this class." *See* JTX0002-0011.

27. The joint specification also discloses the IC50 values for Compound 338 of 5 nM for CDK4, >1.6 μM for CDK1, and >1.4 μM for CDK2, and cell cycle analysis results for Compound 338. JTX0002-0011-0012; Tr. 93:2-10, 211:21-213:10 (Micalizio); JTX0004-0011-0012; *see also* JTX0007-4315 (correcting IC50 values for "prior art" compounds in Table 4 during patent prosecution).

28. The Brain PCT provided IC50 values for Compound 338 of >1 μM for CDK4, <10 μM for CDK1, and <10 μM for CDK2. JTX0042-0198; Tr. 92:17-93:5 (Micalizio).

B. A POSA Would Have Selected Compound 338 as a Lead Compound for Modification Based on the Pfizer SAR Papers

29. A POSA would have known that a lead molecule for a selective CDK4 inhibitor should have an IC50 potency against CDK4 in the single-digit to low double-digit nanomolar range. Tr. 67:24-68:9 (Micalizio).

30. Compound 338 has an IC50 potency against CDK4 within the desired range. JTX0002-0011; Tr. 93:12-20 (Micalizio).

31. A POSA would use the data for Compound 338 in Brain PCT as a guide to select a lead compound. Tr. 159:21-160:15 (Micalizio), 383:18-25 (Toogood).

32. A POSA would have understood that although Compound 338 was not among the most selective, it was among the most potent CDK4 inhibitors disclosed in Brain PCT. JTX0042-0198; Tr. 92:17-93:5; 93:21-23, 159:21-160:11, 160:25-161:13, 197:2-11 (Micalizio), 384:18-385:11, 391:4-21 (Toogood).

33. A POSA knew that palbociclib is a potent and selective CDK4 inhibitor. *Supra.* ¶ 11. A POSA would have looked to the available palbociclib information when pursuing a new CDK4 inhibitor and been motivated to achieve at least the selectivity disclosed in the Pfizer SAR Papers. Tr. 372:20-373:17, 470:7-15, 490:11-491:12, 499:1-6, 501:24-502:16 (Toogood).

34. From the Pfizer SAR Papers, a POSA would have known that a potent CDK4 inhibitor should interact with the four sub-regions of the ATP binding site. *Supra.* ¶¶ 6-10; *see also* Tr. 62:9–64:4, 64:24–65:23, 66:6-67:8, 68:10–69:21, 74:22–76:10, 76:25-78:3, 82:8-23, 83:2–84:9 (Micalizio); JTX0021-0003 (l. col., ¶4-r. col., ¶1), -0004 (1. Col., ¶2- r. col., ¶1; Tables

3 and 4); JTX0096-0006 (¶2, FIG. 7); JTX0099-0003 (r. col., ¶3)-0004 (l. col., ¶1-2 and Table 3), -0005 (Table 4); JTX0094-0003 (l. col., ¶4-r. col., ¶ 1; Table 1-2), -0005 (l. col., ¶1).

35. A POSA would have understood that Compound 338 contains all the structural motifs disclosed in the Pfizer SAR Papers, and that such teachings could be applied to Compound 338. Tr. 95:2-100:18, 203:24-205:15 (Micalizio).

36. A POSA would have known from the Pfizer SAR Papers that selectivity for a CDK4 inhibitor could be improved on potent (but non-selective) CDK4 inhibitors by replacing a phenyl group at C2 with a pyridyl group. JTX0094-0002 (l. col, ¶2), -0003 (l. col., ¶3); Tr. 79:9-80:1, 80:21-82:7, 205:16-206:6 (Micalizio).

37. A POSA reading the Pfizer SAR Papers would have recognized that Compound 338 is a lead compound for further modifications, because it is structurally similar to palbociclib and it was disclosed as a potent, but relatively non-selective, CDK4 inhibitors. Tr. 92:17-94:9, 165:10-15, 197:20-199:5, 208:19-209:1 (Micalizio).

C. A POSA Would Have Been Motivated to Use a Pyridyl to Modify Compound 338 to Achieve Ribociclib, with a Reasonable Expectation of Success

38. Compound 338 was known to possess the molecular features that made palbociclib a potent and selective CDK4 inhibitor, except the pyridyl group at C2. *Supra.* ¶ 34; Tr. 95:2–96:5 (Micalizio).

39. Moreover, a POSA would have understood from Toogood 2005 that palbociclib displayed "a superior overall profile, including the combined attributes of potency, selectivity, and pharmaceutical properties," and explained that the pyridyl group's nitrogen off the C2 position was the key factor for palbociclib's selectivity. JTX0094-0006 (r. col., ¶1, 3). A POSA would have further appreciated that the effect of the nitrogen in the C2 pyridyl group "appears to be general and to apply across a wide range of kinases." *Id.*

40. This knowledge regarding the effect of the nitrogen on the C2 pyridyl group would have motivated a POSA to modify Compound 338 to replace the C2 phenyl with a pyridyl with a reasonable expectation of achieving a CDK4 inhibitor with superior properties, including selectivity for CDK4. Tr. 104:15–106:9 (Micalizio).

41. A POSA would have been capable of overlaying the structure of Compound 338 with palbociclib to determine that the C2 side chain in both compounds would lie within the same region, the specificity surface of CDK4's ATP binding site. Tr. 106:10–107:13 (Micalizio).

42. Accordingly, a POSA would have reasonably expected that applying the pyridyl substitution at C2, to align with palbociclib from the Pfizer SAR Papers, would confer the same general benefit. Tr. 105:16–106:12 (Micalizio).

43. Although the prior art disclosed that the C2 pyridyl may slightly decrease potency for CDK4, several examples taught a POSA that such a drop resulted in a single-digit nanomolar to low double-digit nanomolar, still within the desired range. Tr. 68:5-9, 107:14–108:13 (Micalizio); *see also* JTX0094-0003-4 (*compare* FIGS. 3 and 4 and *compare* FIG. 5 *with* Table 3); Tr. 499:18–503:15 (Toogood).

44. From the prior art, a POSA would have also understood that preferred compounds would have a balance between potency and selectivity, which "suggested that the optimal inhibitor may not be the post potent." JTX0099-0004 (l. col., ¶2); Tr. 108:2–13 (Micalizio). Accordingly, a POSA would have known that a small loss of potency in favor of a large gain in selectivity was a desirable modification. Tr. 108:2–13 (Micalizio); JTX0099-0004 (l. col., ¶2).

45. Thus, even if an expectation of some decrease in potency may have existed, a POSA would have still been motivated to modify Compound 338 with a reasonable expectation of success. Tr. 108:2–13 (Micalizio); JTX0099-0004 (l. col., ¶2).

D. Claim 6 of the '630 Patent Is Obvious Over Compound 338 in View of the Pfizer SAR Papers and Fry

46. Claim 6 of the '630 patent is directed to a method of treating carcinoma of the breast by inhibiting CDK by administering ribociclib (or a pharmaceutically acceptable salt thereof). JTX0004-0073.

47. Since 2004, a POSA would have understood that selective inhibitors of CDK4 could be used to treat breast cancer. JTX0093-0001 (r. col, ¶3) and 0009 (r. col., ¶2). Specifically, Fry disclosed that palbociclib exhibited "robust antitumor activity" in a breast carcinoma cell line *in vivo*. JTX0093-0005 (r. col., ¶1); Tr. 109:18-111:12 (Micalizio).

48. Because the motivation to modify Compound 338 is based on a similar modification contained within palbociclib, a POSA would have reasonably expected that the resulting compound, ribociclib, could also be used to treat cancer, including breast cancer. JTX0093-0001 (r. col., ¶3) and 0009 (r. col., ¶2); Tr. 104:15-105:15 (Micalizio).

E. Secondary Considerations Fail to Outweigh *Prima Facie* Obviousness

49. As explained above, a POSA would have expected that the use of a pyridyl at the C2 position of Compound 338 would make it more selective and thus case a G^1 block. Tr. 673:18–676:8 (Micalizio); JTX0094-0005; JTX0149-0020. A POSA also would have expected ribociclib, containing the same C2 pyridyl, to have a similar profile and clinical effectiveness. JTX0093-0001(r. col., ¶3)-0005 (r. col., ¶1), -0009 (r. col., ¶2); Tr. 104:15-105:15, 109:18-111:12 (Micalizio).

50. It is undisputed that a POSA would have expected that a drug would be efficacious for its clinical trial endpoints. Tr. at 604:24-605:4 (Cohen).

51. Plaintiffs' expert, Dr. Cohen, did not rely on any references to support existence of a long-felt need that pre-date the '355 and '630 patents' priority date. *See* JTX0162; JTX0268; DTX070; PTX677; JTX0258; JTX0277; JTX0260; JTX0081.

52. Dr. Cohen could not have relied on his experience as an oncologist to establish a need, because he was not an oncologist until 2010, two years after the priority date. Tr. at 583:17-584:6 (Cohen).

53. At trial, Dr. Cohen introduced new long-felt but unmet need opinions that had not been previously disclosed. Tr. at 541:18-542:6 (Cohen); *compare* 541:18-542:4 (Cohen) *with* D.I. 111, Ex. R at MIL No. 1, Ex. A at ¶ 94.

54. It is undisputed that there remains a need in the art to cure breast cancer, specifically metastatic breast cancer. Tr. at 614:16-23 (Cohen).

55. Plaintiffs' expert, Dr. Toogood, has no knowledge or references that exhibit why other members of industry opted not to litigate the patents-in-suit and why others chose not to continue their CDK inhibitor programs. Tr. at 475:2-8, 513:14-514:13 (Toogood).

56. Plaintiffs' expert, Dr. Cohen, did not apply any legal standard to his analyses of skepticism of others and industry praise. Tr. at 593:23-594:5, 597:9-18 (Cohen).

57. Plaintiffs' expert, Dr. Vellturo, did not consider relevant marketing and other expenses associated with Kisqali and neglected to consider unasserted patents listed in the Orange Book for Kisqali. Tr. at 656:18-22, 666:13-667:12 (Vellturo), 767:16-768:15 (Hofmann).

III. CLAIM 1 OF THE '355 PATENT AND CLAIM 6 OF THE '630 PATENT ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING OVER CLAIM 7 OF THE '225 PATENT IN VIEW OF THE PFIZER SAR PAPERS

A. Claim 7 Encompasses Using the Recited Compounds for Inhibiting CDK4 and Treating Breast Cancer

58. Claim 7 of the '225 patent recites thirty-three compounds. JTX0001-0127-0131.

59. The ’225 patent discloses uses of the recited compounds for inhibiting CDK4 and treating breast cancer. JTX0001-0031 (58:55-60, disclosing that the compounds are “used for the treatment of protein kinase-associated disorders,” which includes “disorders and states . . . that are associated with the activity of a protein kinase, e.g., CDK4 and Jak3.”); JTX0001-0036 (67:49–51, disclosing “The inventive compounds are particularly useful for treating a tumor which is a breast cancer[.]”).

B. A POSA Would Have Selected Compound 338 from the Thirty-Three Compounds Recited in Claim 7

60. A POSA looking at the structures of the compounds of claim 7 would have perceived them as CDK inhibitors because of their structural similarity to palbociclib. Tr. 112:8-25 (Micalizio).

61. The Pfizer SAR Papers also would have led a POSA to narrow the group of thirty-three compounds to two compounds (Compound 338 and Compound 335), due to their similar structural motifs to palbociclib. Tr. 113:1–117:20 (Micalizio). The Pfizer SAR Papers also would have led a POSA to narrow the group of thirty-three compounds to Compound 338 due to its similar structural motifs to palbociclib. Tr. 112:16–119:8 (Micalizio).

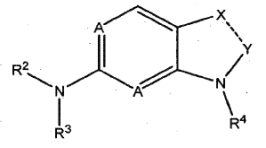
IV. CLAIM 1 OF THE ’225 PATENT IS INVALID FOR LACK OF WRITTEN DESCRIPTION AND LACK OF ENABLEMENT

A. The ’225 Patent’s Claims Are Not Described by the Specification to Show that the Inventors Possessed the Claimed Invention

62. Claim 1 of the ’225 patent defines a genus of compounds. JTX0001-0126-0127.

1. The ’225 Patent Recites a Single Functional Group in a Laundry List of Substituents

63. The ’225 patent’s as-filed claims and specification described a compound having the following formula:



(I)

JTX0006A-1633. The definitions for each group were much broader than in the asserted claim. *See id.* at 1634.

64. During prosecution, the applicants amended the claims such that a dashed line could only be a double bond, X had to be CR^{11}, Y had to be CR^{12}, R^{11} was limited to "hydrogen or C_1-C_3 alkyl," and R^{12} was restricted to only $BC(O)NR^{13}R^{14}$, which remain in the as-issued claim. JTX0001-0126-0127.

65. The specification recited, at filing, twenty-three possible moieties that could be "independently selected" for R^{11} and R^{12}. JTX0006A-1633-1634.

66. Plaintiffs' expert, Dr. Toogood, pieced together elements from four different dependent claims, then picked and chose from the laundry list of moieties alleging "blaze marks" to support claim 1. *See* Tr. 460:6–461:14, 481:21–487:12 (Toogood).

67. In a post-hoc exercise, Dr. Toogood limited the dashed line in the original claim to being a double bond, combined the limitations of original claims 1, 5, and 11, and selected R^{11} as "H or C_1-C_3 alkyl" from twenty-three different options, and R^{12} as $BC(O)NR^{13}R^{14}$ from the same list. Tr. 460:6–461:14, 481:21–487:12 (Toogood).

68. Dr. Toogood also, for the first time ever, attempted to recast the thirty-three disparate compounds from the specification that fall within the claim language as "blaze marks" to the claimed genus. *E.g.*, Tr. 486:18–23 (Toogood).

69. Defendants' expert, Dr. Micalizio, explained that there are not "blaze marks" toward the thirty-three disparate compounds or the claimed subgenus because compounds that fall

inside and outside the subgenus are disclosed as being potent at their biological target. Tr. 137:15–139:3 (Micalizio).

70. Dr. Micalizio explained that the examples in the ’225 patent specification provide a small set of the much larger number of species that fall within the claimed genus, and do not show compounds having all the structural features recited in claim 1. Tr. 138:23–140:16, 140:17–141:20, 141:21–142:12 (Micalizio).

2. There Is a Small Percentage of Species from Claim 1 Described in the Specification

71. The construction of “substituted” in claim 1 results in a potentially infinite scope of the asserted claim. D.I. 111 at Ex. A, ¶ 58; Tr. at 125:8-126:12 (Micalizio).

72. The ’225 patent does not disclose sufficient species to provide support for the full scope of claim 1, particularly the R^3 and R^{12} groups. Tr. 138:23–140:16, 140:17–141:20, 141:21–142:12 (Micalizio). Plaintiffs’ expert, Dr. Toogood, provided no opinion that the thirty-three compounds disclosed in the ’225 patent specification are sufficiently representative to describe the claimed genus, or that the inventors possessed the claimed invention. Tr. 480:7–10 (Micalizio).

B. Claim 1 Is Not Enabled by the Specification

73. The R^3, R^{13}, and R^{14} groups may include “substituted” moieties, which can themselves be further substituted, so the claims encompass an infinite number of compounds. Tr. 120:11–24, 121:16–122:21 (Micalizio); D.I. 74 at 2.

74. The ’225 patent specification provides a long list of substituents using non-limiting language that indicates to a POSA that other unrecited substituents may be included. Tr. 120:25–121:15 (Micalizio); JTX0001-0033 (61:20–62:16).

75. The '225 patent specification discloses that the claimed compounds are useful in treating proliferative diseases and modulating activity of over seventy different kinases in multiple kinase families. *See, e.g.,* JTX0001-0002 and 0031; Tr. 125:8–126:12 (Micalizio).

76. The specification does not instruct a POSA how to choose substituents that result in activity for any particular kinase other than the few examples disclosed for data at CDK1, CDK2, CDK4, and JAK3. Tr. 126:16–24 (Micalizio); *see also* JTX0001–0006–30 (Tables A–C), JTX0001-0125–126 (Table E).

77. Accordingly, a POSA would need to test those examples without activity at the exemplified kinases to determine which, if any, kinases there are activity, and repeat the same for the undisclosed embodiments. Tr. 125:8–126:15 (Micalizio).

78. The specification discloses 450 different molecules, but only thirty-three of these fall within the scope of claim 1. Tr. 127:3–128:14 (Micalizio).

79. Claim 1 recites R^3 can be "substituted C_3-C_8 cycloalkyl [or] substituted heterocyclyl," but there are no examples of compounds bearing these R^3 groups and only two examples show compounds where R^3 is a one-carbon linker substituted with an aryl group. Tr. 128:15–129:19 (Micalizio).

80. The approximately sixteen examples from the patent where the R^3 group is something other than a substituted aryl or heteroaryl have limited examples of any biological activity. Tr. 129:20–131:15 (Micalizio).

81. There is limited variability at the R^{12} position for the disclosed examples, because: B is only ever a bond, when R^{13} and R^{14} are both anything other than hydrogen they are only methyl groups, and there are no examples of R^{13} and R^{14} as C_3-C_8 cycloalkyl, substituted C_1-C_3 alkyl, substituted C_3-C_8 cycloalkyl, or substituted heterocyclyl. Tr. 131:16-132:25 (Micalizio).

82. Plaintiffs' expert, Dr. Toogood, offers no opinion as to the quantity of experimentation required to identify the useful compounds covered by claim 1 of the '225 patent. Tr. 478:2-18 (Toogood).

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on March 1, 2024, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF (which will send notification that such filing is available for viewing and downloading to all registered counsel), and in addition caused true and correct copies of the foregoing document to be served upon the following counsel of record by electronic mail:

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March 1, 2024

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